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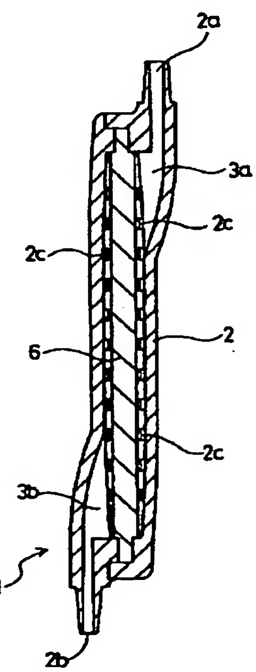
(54)【発明の名称】　白血球分離用フィルターおよび白血球除去器

(57)【要約】

【目的】　白血球または血小板に対して、高くてかつ安定した捕捉能を有し、血液中より短時間に効率よく白血球または血小板を分離することができ、また、操作時における異物の流出のおそれがなく安全で、さらに、製造が容易で、かつ製品の性能のバラツキの少ない白血球分離用フィルター、または白血球および血小板分離用フィルターを提供する。

【構成】　この白血球分離用フィルターは、最頻孔径が１～５μmで、かつ、量平均孔径と数平均孔径との比が１．５～２．５である三次元網目状連続多孔体により形成されている。



Original document

LEUKOCYTE SEPARATION FILTER AND LEUKOCYTE REMOVER

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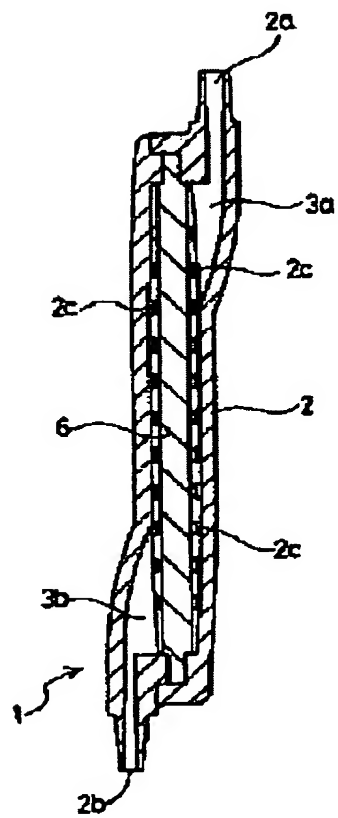
Abstract of **JP7124255**

PURPOSE:To prepare a leukocyte separation filter having freedom from a concern about the outflow of a foreign substance at the time of operation and a high and stable collection function for leukocyte by forming the filter out of a three-dimensional mesh type continuous porous body having a specific value as a most frequent hole diameter, and another specific value as a ratio of a quantitative mean hole diameter to a numerical mean hole diameter. CONSTITUTION:A leukocyte remover 1 using a leukocyte separation filter 6 is formed out of a housing having a blood inflow port 2a and a blood outflow port 2b, and a leukocyte separation filter 6 laid so as to divide the internal space of the housing 2 into a blood inflow section 3a and a blood outflow section 3b. Also, the filter 6 is formed out of a three-dimensional mesh type continuous porous body having a value between 1 and 5mum as a most frequent hole diameter, and a value between 1.5 and 2.5 as a ratio of quantitative mean hole diameter to numerical mean hole diameter. The filter 6 so formed has a high and stable collection function for leukocyte, and the leukocyte contained in blood, when passing a complicated flow passage between the matrices of the porous body, is efficiently collected in a short time.



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This invention relates to filters for separating leukocytes, leukocyte removers, filters for separating both leukocytes and platelets, and leukocyte/platelet removers. It is concerned to provide those having an excellent capability for capturing

leukocytes without suffering from contamination with foreign matter.

In recent years, blood transfusion has largely changed from conventional whole blood transfusion to blood component transfusion, in which only a necessary component is transfused to a patient. An important problem in blood component transfusion is how to increase the purity of respective fractionated blood components.

Blood from donors has conventionally been centrifugally separated into concentrated red cells (CRC), a platelet concent (PC), and a platelet-poor plasma (PPP). Blood preparations obtained by the separation of blood are used for blood comp transfusion to patients who need red cells or platelets. However, since a large amount of leukocytes are contained in bloc preparations, problems may sometimes occur if a large amount of leukocytes are introduced into patients by transfusion.

Leukocytes contained in blood preparations must be removed as far as possible for the purpose of avoiding side effects, particularly post-transfusion reactions. To date, a number of improvements have been proposed for this purpose. In some extraction of red cells alone by excluding leukocytes and platelets is also required. Used for these purposes are a method capturing member, a gravitational centrifugal separation method utilizing the difference in specific gravity between bloo a method utilizing the viscidity or adhesion of leukocytes, etc.

Among them, the method using a capturing member is widely used because of good efficiency in removing leukocytes o leukocytes and platelets, easiness of handling, etc. Capture members often used are fibers having extremely small diame such as natural fibers, synthetic fibers, etc. packed into a column, or non-woven fabrics formed by secondarily processin

The use of such fibers, however, is likely to suffer from detachment of some fibers or outflow of foreign matters during operation. If the fiber packing density is increased for the purpose of sufficiently capturing leukocytes or platelets, trapp cells tend to clog pores between the fibers.

On the other hand, there are various proposals to use porous members as the capturing members. For example, Japanese Publication No. 61-39060 discloses the use of a porous member including continuous fine pores with an average pore di of 25 mu m to 60 mu m to capture highly viscous monocytes and granulocytes. Japanese Patent Publication No. 63-2608 discloses a method using a porous member having continuous pores with an average pore diameter of 5 mu m to 20 mu capture leukocytes by utilizing the viscidity of white cells and by filtration with the fine pores of the porous members.

However, in view of the recent demand for more effective removal of leukocytes, the above porous members having rel large pore diameters do not provide satisfactory leukocyte separation. Leukocyte-separating abilities are elevated by red the pore diameter (for example, by reducing the average pore diameter to less than mu m or so); however, blood cells tra are likely to clog the pores of the porous members, taking much time for filtration.

Thus, there have so far been no leukocyte filters, leukocyte/platelet-separating filters, and removers comprising such filt sufficient performance for the practical purpose, and their improvements are still desired.

It is therefore an object of the present invention to provide a leukocyte-separating or leukocyte/platelet filter suffering fr outflow of foreign matters during operation, having a high and stable capability of capturing leukocytes, and capable of efficiently and quickly separating leukocytes, or leukocytes and platelets, from blood or blood preparations.

Another object of the present invention is to provide a leukocyte or leukocyte/platelet remover comprising such a filter.

The first filter according to the present invention comprises a three-dimentionally reticular, porous member with continu open pores having a most frequent pore diameter in the range of 1 mu m to 5 mu m and a ratio of a weight-average pore diameter to a number-average pore diameter in the range of 1.5 to 2.5.

A leukocyte/platelet-separating filter embodying the present invention comprises a laminate of at least one platelet-nonadsorbing, three-dimentionally reticular, porous member with continuous open pores having a most frequent pore di in the range of 1 mu m to 5 mu m and a ratio of a weight-average pore diameter to a number-average pore diameter in th of 1.5 to 2.5, and at least one platelet-adsorbing, three-dimentionally reticular, porous member with continuous open por having a most frequent pore diameter in the range of 1 mu m to 5 mu m and a ratio of a weight-average pore diameter to number-average pore diameter in the range of 1.5 to 2.5.

A leukocyte remover embodying the present invention comprises a housing having a blood inlet and a blood outlet; and or filter laminate as defined above disposed in the housing such that it partitions the interior of the housing into a blood i portion and a blood outlet portion.

In the drawings:

Fig. 1 is front elevational view showing a leukocyte remover including a leukocyte-separating filter according to an emb of the present invention;
Fig. 2 is a right side elevational view of Fig. 1;
Fig. 3 is a cross-sectional view taken along the A-A line in Fig. 1;

Fig. 4 is a front elevational view showing a leukocyte/platelet remover including a leukocyte/platelet-separating filter ac to an embodiment of the present invention;
Fig. 5 is a right side elevational view of Fig. 4;
Fig. 6 is a cross-sectional view taken along the B-B line in Fig. 4;
Fig. 7 is a schematic view showing a circuit including the leukocyte-separating filter according to the present invention;
Fig. 8 is a schematic view showing another circuit including the leukocyte-separating filter according to the present inve
Fig. 9 is a schematic view showing a circuit including the leukocyte/platelet-separating filter according to the present in
Fig. 10 is a schematic view showing another circuit including the leukocyte/platelet-separating filter according to the pre invention; and
Fig. 11 is a schematic view showing an experimental circuit with a leukocyte-separating filter used in Examples and Comparative Examples.

Embodiments of the present invention will be described below in detail.

[1] Leukocyte-separating filter

A leukocyte-separating filter explained in this Section is one for separating leukocytes alone. A filter for separating both leukocytes and platelets will be explained in Section [2].

The leukocyte-separating filter is composed of a three-dimensionally reticular, porous member having continuous open j whose most frequent pore diameter is 1 mu m to 5 mu m. If the most frequent pore diameter is smaller than 1 mu m, oth cells contained in blood or a leukocyte suspension to be treated are also captured during leukocyte removal operation, pc clogging the filter. On the other hand, if the most frequent pore diameter is larger than 5 mu m, the frequency of contact leukocyte suspension to be treated is lowered, possibly decreasing the blood cell capturing rate. The more preferable mo frequent pore diameter of the leukocyte-separating filter is 2 mu m to 4 mu m.

The term "most frequent pore diameter" used herein means a pore diameter which the largest number of pores have, and defined as a most frequently occurring diameter (peak value) in a distribution of pore diameters. The pore diameter distr is obtained by cutting a porous member along an arbitrary surface, measuring cross section areas of respective pores dist throughout the entirety of the cross section surface, calculating diameters of the pores assuming that they are converted i circular pores, and plotting the pore diameters on a graph in which the abscissa indicates pore diameters at 1- mu m-inte and the ordinate indicates the number of pores in every interval (every 1 mu m). Thus, the most frequent pore diameter i a pore diameter most often shown, regarding all of the pores having variable shapes and diameters as circular cross-secti pores.In order to ensure a reliability, not less than 2000 pores are preferably measured at random.

By the foregoing definition, the most frequent pore diameter does not necessarily represent the largest diameter among t the existing pores, but merely means that the number of pores having larger or smaller diameters than the most frequent diameter gradually decreases. Therefore, the most frequent pore diameter does not even mean that particles having large diameters do not pass through the porous member. Although red cells in general have larger diameters than the most fre pore diameter, living red cells can freely deform and pass through the pores.

The porous member constituting the leukocyte-separating filter is characterized by having an average pore diameter ratic of a weight-average pore diameter to a number-average pore diameter) of 1.5 to 2.5. If the average pore diameter ratio is than 1.5, clogging is liable to occur, and filtration takes much time. If it exceeds 2.5, the capturing rate is liable to decrea

The weight-average pore diameter is a value defined by SIGMA Ri<2>Ni/ SIGMA RiNi similarly to the equation of the average molecular weight, and the number-average pore diameter is a value defined by SIGMA RiNi/ SIGMA Ni, wher pore diameter measured by a mercury infiltration method, and Ni is the number of pores having a diameter Ri. The pore diameter Ri is determined by randomly cutting a porous member, measuring cross section areas of respective pores distr throughout the entirety of the cross section surface, converting the cross sections of the pores to circles, and calculating diameters of the circles. As explained above, the average pore diameter ratio represents a distribution of pore diameters. larger the value of the average pore diameter ratio, the wider the distribution of pore diameters, meaning that there are m pores having larger diameters than the most frequent pore diameter and many pores having smaller diameters than the m frequent pore diameter.

The porosity of a platelet-nonadsorbing, three-dimensionally reticular, porous member with continuous open pores is pr 75% to 95% and more preferably 80% to 95%, although it may vary depending on the most frequent pore diameter, etc. the porosity is 75% or more, leukocytes are removed in a short time. If the porosity is 95% or less, a sufficient strength r for a filter is obtained. The thickness of the porous member is preferably 0.1 mm to 10 mm and more preferably about 0. about 3 mm, although it may vary depending on the most frequent pore diameter, porosity and microstructure of the por member. If the porous member is 0.1 mm or thicker, the filter is strong enough. On the other hand, if it is 10 mm or thin length of filtration path is not excessive, and clogging is unlikely to occur.

The leukocyte-separating filter may be composed either of a single porous member in the form of a flat sheet or of a plui such porous members. Preferably, however, a plurality of flat porous members are stacked to provide a laminate. In case the leukocyte-separating filter is composed of a plurality of porous members, it is preferred to dispose one or more porou members having wider pore diameter distributions (larger average pore diameter ratios) on the upstream side and one or porous members having narrower pore diameter distributions (smaller average pore diameter ratios) on the downstream : Placing the porous member having a wider pore diameter distribution on the upstream side provides efficient separation leukocytes without increasing filtration resistance.

The three-dimensionally reticular, porous member with continuous open pores constituting the leukocyte-separating filte having the above characteristics is made of a platelet-nonadsorbing material. The term "platelet-nonadsorbing" used here means a characteristic of adsorbing substantially no platelet, and does not necessarily mean absolute non-adsorption of p Preferable materials therefor are ethylene-vinyl alcohol copolymers, polyurethanes of any types including a polyether ty polyester type and a polycarbonate type (preferably polyurethanes containing polyethers such as polytetramethylene oxi polypropylene oxide or polyethylene oxide), fluorocarbon polymers (preferably polyvinylidene fluoride), polysulfones, ; polyether sulfones. Particularly preferable are polyurethanes.

A preferable method for manufacturing the porous member is a so-called elution method which comprises extruding a fl made of a resin composition including a polymer such as polyurethane, polyvinylidene fluoride, polysulfone, polyester, polyamide, etc., a good solvent therefor and a pore-creating agent soluble in or swellable with a non-solvent having a compatibility with the good solvent, and then immersing the extruded flat sheet in the non-solvent to cause gelation whil eluting out the pore-creating agent, thereby forming a flat porous sheet or film having "through-pores," pores penetrating one side to the other of the porous sheet or film. A preferable ratio of the polymer in the resin composition is 5 weight % weight %.Preferable good solvents are dimethyl formamide, dimethyl sulfoxide, acetone, dioxane, methyl Cellosolve ac tetrahydrofuran, ethyl alcohol, methyl alcohol, methyl ethyl ketone, etc. Preferable pore-creating agents are polyvinyl al polyvinyl pyrrolidone, methyl cellulose, polyether, polysaccharide, polyacrylic acid, etc. A preferable amount of the por creating agent added is 5 weight % to 50 weight % based on the composition to provide the porous member with contin open pores (fine through-pores). This manufacturing method is described in detail in Japanese Patent Laid-open No. 3-4 the case of polyurethane, it may be coated on another material.

Since the leukocyte-separating filter of the present invention exhibits a high and stable capability of capturing leukocyte: efficiently and quickly separate leukocytes from a platelet concentrate (PC), concentrated red cells (CRC) or a whole blc without danger of outflow of foreign matters during operation. Further, the leukocyte-separating filter suffers from little in performance.

[2] Filter for Separating Leukocytes and Platelets

A filter for separating leukocytes and platelets (leukocyte/platelet-separating filter) may be either composed of one or m platelet-adsorbing, three-dimensionally reticular, porous member with continuous open pores, or of a laminate of one or platelet-nonadsorbing, three-dimensionally reticular, porous members with continuous open pores and one or more plate adsorbing, three-dimensionally reticular, porous members with continuous open pores. In any case, the porous members most frequent pore diameter of 1 mu m to 5 mu m and an average pore diameter ratio (ratio of a weight-average pore dia a number-average pore diameter) of 1.5 to 2.5 in order to have a good leukocyte-separating capability. For the same reas stated above, the most frequent pore diameter is preferably 2 mu m to 4 mu m.

The platelet-nonadsorbing, three-dimensionally reticular, porous member with continuous open pores may be the same a explained in [1] above. In contrast, the platelet-adsorbing, three-dimensionally reticular, porous member with continuou: pores may be made either of a platelet-adsorbing material or of a cationic-treated platelet-nonadsorbing or platelet-adsor material.

Platelet-adsorbing materials usable in the present invention are polyvinyl acetals (preferably polyvinyl formal), aliphatic polyamides which may be nylon 6, nylon 66, nylon 12, or so-called polyetheramides copolymerized with polyether com such as polytetramethylene oxide, polypropylene oxide and polyethylene oxide, aromatic polyamides (preferably, in par polymethaphenylene isophthalic amide or polyparaphenylene terephthalic amide), polyesters (in particular polybutylene terephthalate, polyethylene terephthalate, etc.), polyimides, etc.

The term "cationic treatment" used herein means to adhere or bond a cationic compound to a surface of a filter substrate incorporate the cationic compound into the filter substrate. Specifically, there are methods of coating the porous membe cationic compound, methods of bonding the cationic compound to the filter substrate by grafting copolymerization, etc., methods of mixing the filter substrate with the cationic compound in the process of fabrication of the porous member. C compounds usable are quaternary ammonium salts, compounds having amino groups or imino groups, etc.For example, preferable method for bonding the cationic compound to the filter substrate by graft copolymerization, the filter substrat subjected to a plasma treatment, and graft-copolymerized with a monomer having a reactive substituent such as glycidyl methacrylate, and then a cationic agent is bonded to the grafted monomer. Cationic treatment contributes to maintaining positive charge of the filter for a long period of time.

The platelet-adsorbing, three-dimensionally reticular, porous member with continuous open pores has a porosity of 75% and a thickness of 0.1 mm to 10 mm for the reason described in [1] above.

The platelet-adsorbing, three-dimensionally reticular, porous member with continuous open pores may be produced by a method, provided that the porous member has the aforementioned structure. A preferable method is an elution method. I case of making the porous member of polyvinyl formal, for example, the elution method uses an acetal-forming reaction which formaldehyde and an acid catalyst acts on an aqueous polyvinyl alcohol solution containing a pore-creating agent from amylose-containing polysaccharide such as starch and dextrin, derivatives thereof, acid-proof anionic surfactants, r surfactants, etc. optionally in the presence of an inorganic salt such as sodium sulfate, sodium chloride, ammonium sulfa ammonium chloride, potassium sulfate, sodium iodide, etc. (Patent Publication Nos. 47-46455 and 48-20019).

With a high and stable capability of capturing leukocytes and platelets, the leukocyte/platelet-separating filter of the pres invention can efficiently and quickly separate leukocytes and platelets from concentrated red cells (CRC) and a whole bl without danger of outflow of foreign matters during operation. It also reduces variance in performance.

[3] Leukocyte Remover

A leukocyte remover equipped with the leukocyte-separating filter according to the present invention will be explained t detail with reference to Figs. 1 to 3. Fig. 1 is a front elevational view of an example of the leukocyte remover with the leukocyte-separating filter according to the present invention, Fig. 2 is a right side elevational view of Fig. 1, and Fig. 3 : cross-sectional view taken along the A-A line in Fig. 1.

The leukocyte remover 1 with the leukocyte-separating filter 6 according to the present invention is composed of a housi having blood inlet 2a and a blood outlet 2b, and a leukocyte-separating filter 6 constituted by a three-dimensionally retic porous member with continuous open pores and disposed in the housing 2 such that it partitions the interior of the housii a blood inlet portion 3a and a blood outlet portion 3b. As shown in Fig. 3, the filter 6 of the present invention is received housing 2 such that blood, etc. introduced into the housing 2 through the blood inlet 2a cannot exit from the blood outlet without passing through the filter 6. A circumferential portion of the filter 6 is water-tightly disposed between inner surf: two members of the housing 2.The filter 6, as shown in Fig. 3, is partly clumped by a plurality of projections 2c formed · inner surface of the two constituent members of the housing 2 to prevent deformation of the filter during operation and s

Usable for the housing 2 are various materials such as polycarbonates, acrylic resins, polyethylene terephthalate, polyeth polypropylene, polystyrene, polyvinyl chloride resins, acryl-styrene copolymers, acryl-butylene-styrene copolymers, anc Particularly preferable are polycarbonates, acrylic resins, polyethylene terephthalate, polyethylene, polypropylene, polys and polyvinyl chloride resins. The inner surface of the housing 2 is preferably treated to have a hydrophilic nature to alle adhesion of blood cells thereto. Suitable hydrophilic treatment is coating or bonding of a hydrophilic substance, or a surl treatment such as plasma treatment, corona treatment, etc.

In the leukocyte remover 1 according to one embodiment of the present invention shown in Fig. 3, a pre-filter portion (tl side portion of the filter 6 in Fig. 3) on the upstream side of a main filter portion (the left side portion of the filter 6 in Fi; functions to remove fine particles in the blood (for example, gels, microaggregates, etc.) and huge leukocyte particles an leukocytes from the blood, before introducing the blood into the main filter portion to prevent clogging of the main filtei portion.

A suitable porous member used for the pre-filter portion is a three-dimensionally reticular, porous member with continu(pores having a most frequent pore diameter of about 2 mu m to about 4 mu m, an average pore diameter ratio of 2.0 to 2. thickness of about 0.3 mm to about 1.5 mm. A suitable number of such porous members laminated is 1 to 5. A suitable p member used for the main filter portion is a three-dimensionally reticular, porous member with continuous open pores h: most frequent pore diameter of about 1 mu m to about 3 mu m and smaller than that of the pre-filter portion, an average · diameter ratio of 1.5 to 2.0, and a thickness of about 0.3 mm to about 1.5 mm. A suitable number of such porous membe laminated is 1 to 5.

In a preferred embodiment, the pre-filter portion may be made by stacking two porous polyurethane films each having a frequent pore diameter of 2.5 mu m to 3.5 mu m, an average pore diameter ratio of 2.5, and a thickness of about 0.6 mm treated by a surfactant, and the main filter portion may be made by stacking four porous polyurethane members each hav most frequent pore diameter of 1.0 mu m to 2.0 mu m, an average pore diameter ratio of 1.7, and a thickness of about 0.(and treated by a surfactant.

The filter may be a single-layered member in lieu of the laminate stated above. The thinner the filter, the easier it is to m integral structure uniform, and the easier the fabrication of a filter meeting the desired numerical conditions. Further, tak intended use, sheet areas and other factors into consideration, any appropriate number of sheets may be laminated to mal desired leukocyte remover. The number of porous sheets laminated may appropriately be determined by considering the rate, filtration time, likelihood of clogging, etc.

Any surfactant may be used for a hydrophilic treatment, and suitably usable are, for example, glycerol monolaurate, and polyether-type surfactants (for example, Pluronic surfactant). Instead of using a surfactant, the porous member may be hydrophilic-treated (for example, plasma-treated).

An example of usage of the leukocyte-separating filter 6 of the present invention will be explained below with reference 7 showing a circuit for removing leukocytes from a blood preparation such as platelet concentrate which does not contai cells for component transfusion of platelets to a patient.

The separation of leukocytes with the circuit of Fig. 7 is started by closing clamps 20a, 20b. Protectors 21a, 21b are then removed, and needles 22a, 22b are attached to a bag (not shown) of a blood preparation (specifically, platelet concentrat a rinse bag (not shown). The blood preparation bag and the rinse bag are hung down from an irrigator (not shown).

While maintaining the leukocyte remover 1 upside down, the clamps 20a and a roller clamp 23 are opened for priming tl leukocyte remover 1. After the priming of the leukocyte remover 1 is completed, the leukocyte remover 1 is returned to original posture. After that, by making an instillator 24 upside down, the blood preparation is introduced into the instillat After the blood preparation occupies about a half volume of the instillator 24, the instillator 24 is returned to the original posture. When the blood preparation reaches a tip end of a lock connector 25, the roller clamp 23 is closed.

With a syringe needle attached to the end of the lock connector 25, instillation (component transfusion, i.e. platelet trans in this case) into the vein of a patient is started. The flow rate of instillation is adjusted by the roller clamp 23.

When the blood preparation bag is emptied, the roller clamp 23 is closed and the clamp 20b is opened to introduce a rins the blood preparation bag. When 100 ml or so of the rinse is introduced, the clamp 20b is closed and the roller clamp 23 opened to resume the component transfusion. When the rinse in the blood preparation bag is exhausted, the rinse in the i tube 27 is recovered by opening an air vent 26, and the transfusion is finished.

Another example of usage of the leukocyte-separating filter 6 of the present invention will be explained below with refe Fig. 8. The circuit of Fig. 8 uses the leukocyte-separating filter 6 of the present invention to remove leukocytes and reco platelets from a blood preparation not including red cells, such as a platelet concentrate. The separation of leukocytes by circuit is substantially the same as that explained above, except for differences in that transfusion using the rinse is cond and that the remover 1 does not include the air vent 12d whose function in the process stated above is performed by an a 37a. Incidentally, transfusion using a rinse may not be conducted in the circuit comprising leukocyte remover 1, and the leukocyte remover 1 may have the air vent 12d.

[4] Leukocyte/platelet remover

A leukocyte/platelet-separating filter and a leukocyte/platelet remover comprising the leukocyte/platelet-separating filte according to the present invention will be explained below with reference to the drawings. Fig. 4 is a front elevation sho example of the leukocyte/platelet remover comprising the leukocyte/platelet-separating filter according to the present in Fig. 5 is a right side elevational view of Fig. 4. Fig. 6 is a cross-sectional view taken along the B-B line in Fig. 4.

The leukocyte/platelet remover 10 comprising the leukocyte/platelet-separating filter 16 of the present invention include housing 12 having a blood inlet 12a and a blood outlet 12b, and the leukocyte/platelet-separating filter 16 disposed in th housing 2 such that it partitions the interior of the housing 12 into a blood inlet portion 1 3a and a blood outlet portion 1 leukocyte/platelet-separating filter 16 is composed of a pre-filter 16a for removing microaggregates and gels occurring i blood, and a platelet-adsorbing, three-dimensionally reticular, porous member with continuous open pores (main filter) 1 having a most frequent pore diameter of 1 mu m to 5 mu m and a ratio of a weight-average pore diameter to a number-a pore diameter in the range of 1.5 to 2.5.With this structure, the main filter 16 exhibits a good ability to capture both leuk and platelets.

The pre-filter 1 6a is preferably composed of non-woven fabrics in the form of a flat sheet each having a weight/area val g/m<2> to 80 g/m<2>, an average fiber diameter of 10 mu m to 20 mu m and a thickness of about 0.3 mm to about 0.6 n Two to five such nonwoven fabrics are preferably laminated. The main filter portion is preferably composed of a primar filter portion having a wider pore diameter distribution and a secondary main filter portion having a narrower pore diam distribution. The primary main filter portion is preferably composed of three-dimensionally reticular, porous members w continuous open pores each having a most frequent pore diameter of about 2 mu m to about 3 mu m, an average pore dia ratio of 1.8 to 2.5 and a thickness of about 0.5 mm to about 2 mm. Two to five such porous members are preferably laminated.The secondary main filter portion is preferably composed of three-dimensionally reticular, porous members w continuous open pores each having a most frequent pore diameter of about 2 mu m to about 3 mu m, an average pore dia ratio of 1.5 to 2.1 and a thickness of about 0.2 mm to about 2 mm. Two to five such porous members are preferably lami The porous members used for the secondary main filter portion may be the same as those used for the primary main filte portion.

In a preferred example, the pre-filter 16a is made by stacking three sheets of non-woven polyester fabrics each having ar average fiber diameter of 12 mu m and a bulk density of 0.1875 g/cm<3> or so to a thickness of about 0.1 mm. An upstr portion of the main filter 16b (the right side portion of the main filter 16b in Fig. 6) constitutes a primary main filter port made by stacking on a 0.2-mm-thick sheet of non-woven polyester fabrics as a support member three surfactant-treated, polyurethane films each having a most frequent pore diameter of 1.0 mu m to 3.0 mu m, an average pore diameter ratio (and a thickness of about 1.0 mm.A downstream portion of the main filter 16b (the left side portion of the main filter 16b 6) constitutes a secondary main filter portion made by stacking three porous polyurethane films identical to those of the upstream portion but subjected to a cationic treatment and a surfactant treatment. Thus, the leukocyte/platelet-separating of the present invention is preferably made by laminating a plurality of such porous members. The number of porous she stacked may be appropriately determined, considering such factors as removal rate, filtration time and likelihood of clog

Any surfactants may be used for a hydrophilic treatment, and suitable surfactants are, for example, deca-glycerol monol: and polyether-type surfactants (for example, Pluronic surfactant). Instead of using a surfactant, the porous member may subjected to a hydrophilic treatment (for example, plasma treatment).

The pre-filter 16a is used to remove microaggregates and gels originally contained in the blood or generated in the blood aggregation during storage. The porous member constituting the primary main filter portion disposed on the upstream si functions to remove leukocytes having larger diameters than its own pore diameters. Negative-charged platelets have sm diameters than those of the porous member constituting the secondary main filter portion disposed on the downstream si Nevertheless, since the porous member of the secondary main filter portion is positive-charged by a cationic treatment, p are electrically trapped by the porous member. Leukocytes passing through the primary main filter portion, although ver are also removed by the secondary main filter portion. Also, red cells having larger diameters than the pore diameters of porous members constituting the primary and secondary main filter portions can pass through the main filter 16b, becaus are easily deformable.

Reasons why the porous member of the main filter 16b is combined with the non-woven fabrics are, among others, that t nonwoven fabrics having little anti-thrombogenic nature function to adsorb highly adherent platelets, that a step for strip them in the sheet fabricating process can be omitted, that the porous member can be more easily mounted in the housing that the non-woven fabrics keep the porous member in a proper shape.

As shown in Fig. 6, the housing 12 of the leukocyte/platelet remover 10 has an air vent 12d near an upper portion. The a 12d facilitates the removal of an air in the course of priming the remover 10, the operation of starting or stopping filtrati recovery of residual liquids in the remover, the removal of an air from the recovery bag, and so forth. Although the air v used in this embodiment can be opened and closed by a cap, it may be configured otherwise.

An example of usage of the leukocyte/platelet-separating filter 16 according to the present invention will be explained b with reference to Fig. 9. The leukocyte/platelet remover 10 with the leukocyte/platelet-separating filter 16 according to t present invention is connected in a circuit as shown, for example, in Fig. 9. The circuit shown in Fig. 9 is for use in com transfusion of red cells to a patient while removing leukocytes and platelets from a whole blood or a blood preparation i red cells (for example, concentrated red cells) by using the leukocyte/platelet remover 10 including the leukocyte/platele separating filter 16 according to the present invention.

The process of separation of leukocytes and platelets by this circuit is the same as those stated above, except that transfu operation by a rinse is not performed, and that the air vent 12d of the remover 10 is opened to transfuse red cells remaini the tube on the outlet side to a patient after the blood preparation bag is emptied. The circuit comprising the leukocyte/pl remover 10 may also be used for transfusing operation by a rinse, and the leukocyte/platelet remover 10 may not necess have the air vent 12d.

Another example of usage of the leukocyte/platelet-separating filter 16 of the present invention will be explained with re to Fig. 10. The circuit shown in Fig. 10 is intended to remove leukocytes and platelets and recover red cells from a whol or blood preparations including red cells by using the leukocyte/platelet remover 10 comprising the leukocyte/platelet-se filter 16.

The process of separation of leukocytes by this circuit is conducted by opening a peel tab 30 and attaching a needle 33 o recovery bag 32 to a vent 31, closing clamps 34a, 34b and a cap 14 of the air vent 12d, removing a protector 35, attachin needle 36 to a blood preparation bag (not shown), and hanging it down from an irrigator (not shown).

The clamps 34a and the cap 14 of the air vent 12d are then opened for priming the remover 10. When the blood preparat reaches the air vent 12d, the air vent 12d is closed by the cap 14, and the clamp 34b is opened, thereby starting filtration.

When the blood preparation bag is emptied, a residual blood preparation on the inlet side is recovered by opening the air 37, and a residual blood preparation on the outlet side is recovered by opening the cap 14 of the air vent 12d. The residu preparation in the tube 38 on the outlet side is recovered in the bag 32 by squeezing the tube 38 with roller pincers. If the need for removal of an air from the recovery bag 32, the air can be expelled from the recovery bag 32 through the air ve by moving the air toward the tube 38 and then pressing the recovery bag 32. Sealing the tube 38, the recovery bag 32 is from the circuit to finish the process of separating leukocytes and platelets.

The present invention will be explained in greater detail by way of Examples below without intention of limiting the pre invention thereto.

Examples 1-6, Comparative Examples 1-4

Leukocyte/platelet-separating filters having the construction shown in Fig. 4 were made by using porous polyvinyl form. members having a thickness of 1.3 mm, a filtration area of 50 cm<2>, and most frequent pore diameters and average por diameter ratios shown in Table 1. Since the porous polyvinyl formal members are hydrophilic and platelet-adsorbing, the not subjected to any particular hydrophilic treatment and cationic treatment.

Every two of the porous members shown in Table 1 were stacked to make a leukocyte/platelet-separating filter, which w assembled in a leukocyte/platelet remover as shown in Fig. 6. Each of such leukocyte/platelet removers was mounted to circuit having the structure shown in Fig. 10. 0.5 units of CPD-added concentrated red cells (CRC) obtained from 400 m human blood were caused to flow through the separating filter gravitationally.

The numbers of blood cells in CRC before and after the treatment, and the numbers of red cells and platelets after the tre were measured with an automatic blood cell counter (Sysmex NE-6000 produced by Toa Medical Electronics Co., Ltd.). total numbers of respective blood cell components were measured on a liquid volume basis, and the red cell recovery rat the platelet removal rates were determined.

The numbers of leukocytes after the treatment were measured with a flow cytometer (Cyto-ACE 150 produced by Nippc Bunko K. K.) and a Nageotte hemocytometer. The total number of leukocytes was measured on a liquid volume basis, a removal rate of leukocytes was determined. The results are shown in Table 2.

Table 1

	Porous Member	
No.	Most Frequent Pore Diameter (mu m)	Average Pore Diameter Ratio
Example 1	1.0	2.0
Example 2	2.0	1.9
Example 3	3.5	1.8
Example 4	4.0	1.7
Example 5	4.5	2.5
Example 6	5.0	2.0
Com. Ex. 1	0.5	2.1
Com. Ex. 2	2.0	1.4
Com. Ex. 3	6.0	1.4
Com. Ex. 4	6.0	2.0

Table 2

	Separation Results			
No.	Filtering Time (minute)	Leukocyte Removal Rate (%)	Red Cell Recovery Rate (%)	Platelet Removal Rate (%)
Example 1	14	99.9	97	92
Example 2	12	99.9	97	92
Example 3	11	99.9	97	91
Example 4	10	99.9	97	91
Example 5	8	99.5	98	90
Example 6	10	99.7	98	90
Com. Ex. 1	53	99.9	94	93
Com. Ex. 2	47	99.9	92	92
Com. Ex. 3	6	93.2	99	82
Com. Ex. 4	5	91.0	99	77

Table 2 proves that the leukocyte/platelet-separating filters of Examples 1 to 6 composed of porous members having mo frequent pore diameters in the range of 1 mu m to 5 mu m and average pore diameter ratios in the range of 1.5 to 2.5 exh good leukocyte removal rates in a practical period of time, and that their red cell recovery rates and platelet removal rate better than those of Comparative Examples 1 to 4.

The same experiment was conducted with porous polyurethane members having a porosity of about 87%, a thickness of a filtration area of 50 cm<2>, and most frequent pore diameters and average pore diameter ratios shown in Table 1. As a substantially the same results were obtained. Incidentally, a primary filter portion of the leukocyte/platelet-separating fil produced by stacking three porous polyurethane members subjected to a hydrophilic treatment with glycerol monolaurat (decaglycerin monolaurate). A secondary filter portion of the leukocyte/platelet-separating filter was produced by using same porous members as in the primary filter portion, by subjecting them to a plasma treatment, graft copolymerization glycidyl methacrylate, fixing of a cationic agent (Cationon UK produced by Ipposha Oil & Fat Industries K.K.) and then treatment with glycerol monolaurate, and by stacking three of them. The housing used was configured as shown in Figs. The housing contained the separating filter to form the leukocyte/platelet remover as shown in Fig. 6.

Examples 7-10, Comparative Examples 5-7

A leukocyte/platelet-separating filter shown in Fig. 11 was made by using porous polyurethane members having a thickr 0.6 mm, a filtration area of 3 cm<2>, a porosity of about 87%, and most frequent pore diameters and average pore diame ratios shown in Table 3. The filter included a pre-filter portion made by stacking two such porous members shown in Ta subjected to a hydrophilic treatment with glycerol monolaurate, and a main filter portion made by stacking four such por members treated by glycerol monolaurate like those of the pre-filter portion. The housing used was configured as shown 11, and contained the above separating filter to form a leukocyte remover.

The leukocyte-separating filters of Examples 7 to 10 and Comparative Examples 5 to 7 were incorporated into circuits h the construction shown in Fig. 11 to form experimental circuits. Lymphocyte-containing, platelet-rich plasma (PRP) (pla 3.5 x 10<5>/ mu l - 5.5 x 10<5>/ mu l, and leukocytes: 3.5 x 10<3>/ mu l - 4.5 x 10<3>/ mu l) was prepared by adding s lymphocytes separated by a density-gradient centrifugal separation method to a platelet-rich plasma (PRP) collected fror added fresh blood of healthy humans. The experiment was conducted by passing the lymphocyte-containing PRP throug experimental circuits shown in Fig. 11 at a flow rate of 1 ml/minute.cm<2>.

The numbers of platelets in PRP before and after the treatment and the numbers of leukocytes in PRP before the treatme measured with an automatic blood cell counter (Sysmex NE-6000 produced by Toa Medical Electronics Co., Ltd.), and t number of leukocytes after the treatment was measured with a flow cytometer (Cyto-ACE 150 produced by Nippon Bun K.) and a Nageotte hemocytometer. The total numbers of respective blood cell components were measured on a liquid v basis, and the leukocyte removal rates and the platelet recovery rates were calculated therefrom.The results are shown in 4.
<tb><TABLE> Id=Table 3 Columns=5
<tb>Head Col 1:
<tb>Head Col 2 to 5: Porous Member
<tb>SubHead Col 1>:
<tb>SubHead Col 2 to 3: Pre-filter Portion
<tb>SubHead Col 4 to 5: Main Filter Portion
<tb>
<tb>SubHead Col 1: No.
<tb>SubHead Col 2: Most Frequent Pore Diameter
<tb>SubHead Col 3: Average Pore Diameter Ratio
<tb>SubHead Col 4: Most Frequent Pore Diameter
<tb>SubHead Col 5: Average Pore Diameter Ratio
<tb><SEP>Example 7<SEP>3.5 mu m<SEP>1.8<SEP>1.0 mu m<SEP>2.0
<tb><SEP>Example 8<SEP>3.5 mu m<SEP>1.8<SEP>2.0 mu m<SEP>1.9
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<tb><SEP>Example 10<SEP>4.5 mu m<SEP>2.5<SEP>1.0 mu m<SEP>2.0
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<tb><SEP>Com.Ex. 7<SEP>6.0 mu m<SEP>2.0<SEP>2.0 mu m<SEP>1.4
<tb></TABLE> EMI27.1

Table 4 proves that the leukocyte filters of Examples 7 to 10 composed of porous members having most frequent pore di in the range of 1 mu m to 5 mu m and average pore diameter ratios in the range of 1.5 to 2.5 exhibited better leukocyte r rates and platelet removal rates than those of Comparative Examples 5 to 7.

As explained above, since the leukocyte-separating filters of the present invention are composed of three-dimensionally reticular, porous member with continuous open pores having most frequent pore diameters ranging from 1 mu m to 5 mu they exhibit high and stable abilities to capture leukocytes. Thus, leukocytes contained in the blood are efficiently and qu captured when passing through complicated flow paths of continuous open pores in the matrix of the porous member. B meeting the requirement that the ratio of a weight-average pore diameter to a number-average pore diameter is in the ran 1.5 to 2.5, the leukocyte removal rate is further improved. Since the flow path of the filter is defined by the three-dimens reticular, continuous texture of a porous member (continuous open pores defined by the matrix of the porous member), t

is stable and uniform in performance. The filter also suffers from substantially no outflow of foreign matters from the po members and channeling of the flow paths during operation. Moreover, since the flow paths of the filter are formed at th of production of the porous member, the filter can very easily be fabricated.

Claims of corresponding document: **EP0630675**

1. A leukocyte-separating filter composed of a three-dimensionally reticular, porous member with continuous open pore: a most frequent pore diameter in the range of 1 mu m to 5 mu m and a ratio of weight-average pore diameter to number-. pore diameter in the range of 1.5 to 2.5.

2. The leukocyte-separating filter according to claim 1, wherein said porous member does not adsorb platelets.

3. The leukocyte-separating filter according to claim 2, wherein said filter is composed of a plurality of said three-dimen reticular, porous members with continuous open pores, and wherein one or more of said porous members located on the upstream side are larger in a ratio of weight-average pore diameter to number-average pore diameter than the remaining members located on the downstream side.

4.A leukocyte/platelet-separating filter comprising a platelet-adsorbing, three-dimensionally reticular, porous member w continuous open pores having a most frequent pore diameter in the range of 1 mu m to 5 mu m and a ratio of weight-ave pore diameter to number-average pore diameter in the range of 1.5 to 2.5.

5.A leukocyte/platelet-separating filter comprising a laminate of at least one platelet-nonadsorbing, three-dimensionally reticular, porous member with continuous open pores having a most frequent pore diameter in the range of 1 mu m to 5 ı and a ratio of weight-average pore diameter to number-average pore diameter in the range of 1.5 to 2.5, and at least one] adsorbing, three-dimensionally reticular, porous member with continuous open pores having a most frequent pore diame the range of 1 mu m to 5 mu m and a ratio of a weight-average pore diameter to number-average pore diameter in the rai 1.5 to 2.5.

6. The leukocyte/platelet-separating filter according to claim 5, wherein said platelet-nonadsorbing porous member is lo(the upstream side and said platelet-adsorbing porous member is located on the downstream side.

7.The leukocyte/platelet-separating filter according to claim 6, wherein said porous member located on the upstream sid(larger in a ratio of weight-average pore diameter to number-average pore diameter than said porous member located on t downstream side.

8. The leukocyte/platelet-separating filter according to claim 5, wherein said platelet-adsorbing porous member is locate upstream side and said platelet-nonadsorbing porous member is located on the downstream side.

9. The leukocyte/platelet-separating filter according to claim 8, wherein said porous member located on the upstream sid larger ratio of weight-average pore diameter to number-average pore diameter, and said porous member located on the downstream side has a smaller ratio of weight-average pore diameter to number-average pore diameter.

10.The leukocyte/platelet-separating filter according to claim 5, wherein said platelet-nonadsorbing porous member is lo the upstream side and has a smaller ratio of weight-average pore diameter to number-average pore diameter, and said pl adsorbing porous member is located on the downstream side and has a larger ratio of weight-average pore diameter to nu average pore diameter.

11. A leukocyte remover comprising a housing having a blood inlet and a blood outlet; and a leukocyte-separating filter according to any one of claims 1 to 3 disposed in said housing such that it partitions the interior of the housing into a blo portion and a blood outlet portion.

12. A leukocyte/platelet remover comprising a housing having a blood inlet and a blood outlet; and a leukocyte/platelet-separating filter according to any one of claims 4 to 10 disposed in said housing such that it partitions the interior of the l into a blood inlet portion and a blood outlet portion.